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Cocrystal engineering of pharmaceutical solids: therapeutic potential and challenges

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Cocrystals are an emerging class of crystalline materials composed of two or more different molecules in the same crystal lattice that are physically connected by non-ionic and non-covalent bonds. Formulating problematic drugs into cocrystals is a pragmatic strategy to manipulate solid state properties for new drug development and product reformulation. While research on cocrystals has been undergoing rapid growth over the past two decades, successful clinical translation of cocrystals is still limited. As the pharmaceutical properties of a cocrystal are decidedly dictated by the selection of cocrystal formers and resulting crystal structure, the present review begins with an overview of the current strategies in cocrystal design and preparation, followed by the potential applications of cocrystals in medicines. The major hurdles and missing knowledge gaps hindering the translation of pharmaceutical cocrystals into commercial reality are also mentioned. Finally, perspectives of cocrystals in alternative dosage forms other than for oral use, as well as latest topics of cocrystal research are highlighted. We believe that cocrystals play an important role in future drug discovery and development, offering a new direction for optimal drug delivery, combination therapy and personalized medicines.

1. Pharmaceutical cocrystals: an overview

Pharmaceutical cocrystals are homogeneous crystalline materials incorporating two or more different molecules, with at least one of them being an active pharmaceutical ingredient (API), in a definite stoichiometric ratio where they are physically connected by non-ionic and non-covalent bonds, including hydrogen bonds.[1,2] Recent advances in cocrystallization are gaining tremendous impetus for its use in modulating a variety of physicochemical and pharmaceutical properties of drugs, such as solubility, dissolution rate, bioavailability, stability, and manufacturability.[3–8] Cocrystallization offers unique advantages over other crystal engineering techniques in reviving old small molecule drugs that are facing obsolescence due to the introduction of alternatives with better tolerance and efficacy to the market. When biologics are expected to dominate future pharmaceutical pipelines, the reformulation of relatively lower priced small molecules *via* cocrystallization has a positive impact on patient access and illustrates how modern crystal engineering can help achieve a principle of cost-effectiveness.

The success of this formulation strategy is witnessed by the exponential increase of novel cocrystals being reported in the literature in the past two decades. The number of cocrystal-related patent submissions surged by seven-fold throughout 2004 to 2016.[9] As intellectual property, pharmaceutical cocrystals generate ample opportunities for inventors to extend the drug lifecycle.[9,10] Recent revision in the FDA regulatory guideline of pharmaceutical cocrystals for the industry, which recognizes cocrystal as a drug product intermediate instead of a new drug substance, is expected to further facilitate the expedition of commercial cocrystal drug products.[2]

Apart from salvaging poorly soluble drugs, the availability of a large library of pharmaceutically accepted coformers leads to a high flexibility in developing cocrystal-based combination therapies for personalized multimorbidity management.[11] It is evident that the upcoming focus will shift gradually from drug–excipient cocrystals to drug–drug, drug–nutraceutical, and even drug–cosmeceutical cocrystals (Fig. 1).[12,13] In this review, we highlight the current

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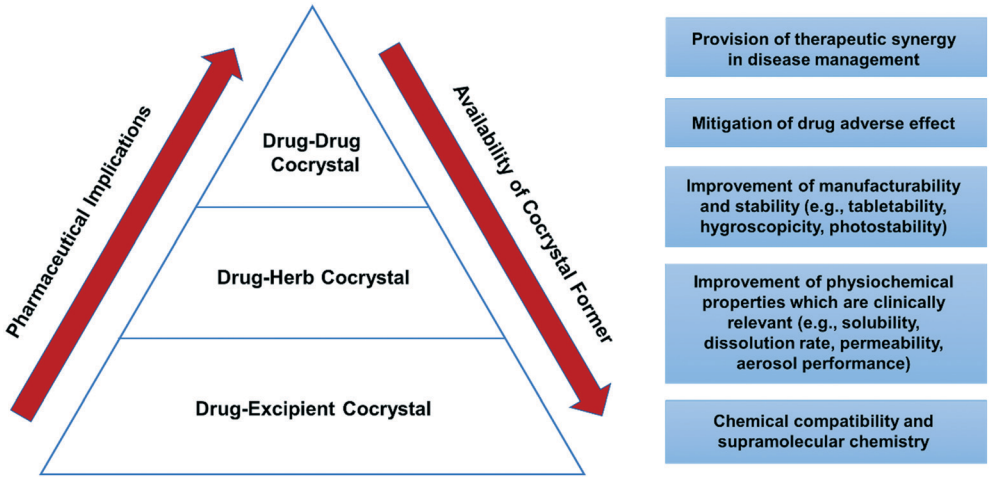

Fig. 1 An overview on the evolutionary development of cocrystals and the corresponding considerations in different stages.

perspectives of cocrystals in medicines, with an emphasis on the discovery and application of pharmaceutical cocrystals. Additionally, the review sheds light on the translational hurdles and the future direction of cocrystal drug product development.

1.1 Cocrystal design and screening

Identification of appropriate coformers is the key to a successful cocrystal development, while being a true "rate-limiting step". The mainstay strategy for cocrystal screening remains as the trial-and-error approach where around 400 substances listed in general regarded as safe (GRAS) can be utilized for cocrystal preparation. The tactless screening process, however, can be costly and time consuming. Alternative techniques based on the pK_a rule,[14] Hansen solubility parameters,[15] supramolecular synthons, structural resemblance,[16] and virtual coformer screening approaches (*e.g.*, conductor-like screening model for real solvents (COSMO-RS), surface site interaction point (SSIP) method, and cloud-computing crystal structure prediction (CSP) based technology[17–23]) have emerged for a more effective cocrystal screening. One should keep an open mind that none of these screening methods would guarantee successful cocrystallization of any API molecule. Instead, they offer complementary advantages in shortlisting potential coformers from large libraries of compounds for developing drug products based on pharmaceutical cocrystals.

1.1.1 The pK_a-based tool. The use of the pK_a rule to predict cocrystal formation is based on the fact that a cocrystal can be distinguished from a salt by whether a proton transfer has occurred from an acid to a base. The pK_a describes the tendency of an acid, or a conjugate acid of a base, to give up a proton. It has been suggested that a ΔpK_a [pK_a(base) − pK_a(acid)] > 3 almost exclusively indicates formation of salt, while a $\Delta pK_a < 0$ predicts cocrystal formation.[14] However, reliable prediction when ΔpK_a is between 0 and 3 cannot be made, a situation commonly found between cocrystal formers with COOH and pyridine functional groups.[24–26] In this intermediate range, salts, cocrystals and even complexes with shared protons or mixed ionization states may form. In fact, based on the ΔpK_a for 6465 crystalline complexes in the Cambridge Structural Database,[27] Cruz-Cabeza reported a linear relationship between ΔpK_a and the probability of proton transfer in the ΔpK_a range of −1 to 4. Because of its simplicity, the pK_a rule has been widely applied for rational selection of coformers to prepare pharmaceutical cocrystals, such as for AMG 517, and a phosphodiesterase-IV inhibitor.[28,29]

1.1.2 Hansen solubility parameter. The prediction of miscibility of a drug and coformer using the Hansen solubility parameter (HSP) gives a clue about cocrystal formability. Group contribution methods by Fedors, Hoy, and Van Krevelen are commonly used to estimate the HSP.[30–32] According to Van Krevelen, two compounds are considered to have good miscibility when their total solubility parameter ($\Delta\delta$) differs by less than 5 MPa$^{0.5}$, regarded as one of the criteria for predicting cocrystal formation.[32] Mohammad *et al.* later suggested that, in order for an API to form a cocrystal, a coformer must be miscible with the API at a molecular level with $\Delta\delta$ less than 7 MPa$^{0.5}$.[15] The HSP has been employed in a number of cocrystal screening studies to guide the selection of coformers, *e.g.*, for synthesizing itraconazole cocrystals.[33] In a study of sulfadimidine–4-aminosalicylic acid cocrystal formation *via* spray drying,[34] it was demonstrated that a large $\Delta\delta$ between the cocrystal formers and the excipient (*e.g.*, microcrystalline cellulose, mannitol) will facilitate cocrystal formation, as the two phases separate from each other owing to immiscibility. A similar HSP between the cocrystal formers and excipients promotes the formation of an amorphous dispersion. The systematic variation of solvents based on the HSP can also influence the cocrystallization outcomes. For example, different polymorphic forms of sulfamethazine–4-aminosalicylic acid were observed when crystallized from eight solvents with different HSPs.[35]

1.1.3 Supramolecular synthons. Supramolecular synthons may be defined as "*structural units found within supramolecules that can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions*".[36] The role of supramolecular synthons was later described as synthetic building blocks for cocrystals, where different types of components were bound together by intermolecular interactions to form a supramolecular system.[37] This concept allowed better recognition of typical molecular arrangements and patterns of binding that can be targeted for cocrystal synthesis.[38] Essentially, a particular synthon may be observed to appear persistently between two functional groups, so cocrystallization of molecules containing those functional groups improves the likelihood of successful cocrystal synthesis. The robustness of a supramolecular synthon can be assessed from analyzing crystal structures in the Cambridge Structural Database (CSD).[39] This approach was used to prepare cocrystals of diacerein,[40] where coformers having amide and pyridine ring functional groups were chosen because a CSD search suggested a high probability of forming a synthon with the complementary carboxylic acid and carbonyl group of diacerein. As all three chosen coformers resulted in successful cocrystals, this serves as a prime example of how supramolecular synthon methods are useful in screening out cocrystals. Supramolecular synthons can be divided into two kinds: (a) heterosynthon: synthons between different but complementary functional groups and (b) homosynthon: synthons between identical and complementary functional groups. Some commonly used supramolecular synthons that confer a high rate of successful cocrystallization include carboxylic acid–acid (33%) and amide–amide (35%) homosynthons, as well as carboxylic acid–pyridine (91%) and carboxamide–carboxylic acid (47%) heterosynthons.[41]

1.1.4 Structural resemblance. On the basis of structural resemblance, one can assume that APIs are more likely to form cocrystals with identical coformers, if successful cocrystallization occurred between the coformers and another API with similar chemical structures. Springuel *et al.* attempted to cocrystallize levetiracetam with a set of acids previously reported to form cocrystals with the racetam compound piracetam.[16] The overall success rate of 40% supported the usefulness of this knowledge-based approach, which was attributed to the presence of similar intermolecular interactions in solution prior to crystallization, as both drugs exhibit a strong negative potential around both amide oxygen atoms and a strong positive potential around the NH_2 group. Likewise, for a given API, cocrystallization behaviors of structurally related coformers with similar functional groups are likely more similar. For example, the use of a series of benzenediols and benzenetriols yielded six curcumin cocrystals with improved dissolution and reduced hygroscopicity.[42] Such structurally guided practice offers a shortcut for efficient cocrystal production based on *a priori* knowledge, which is particularly useful for early drug development when only a small amount of API is available.

1.1.5 *In silico* virtual coformer screening. Computational cocrystal screening methods hold advantages over experimental ones in terms of material-sparing. One virtual cocrystal screening method is the conductor-like screening model for real solvents (COSMO-RS) fluid-phase thermodynamics theory, which describes the miscibility of cocrystal formers in a supercooled liquid phase.[17] In this approach, the cocrystallization tendency is measured by the excess enthalpy (H_{ex}) between an API–coformer mixture relative to the pure components. Because the COSMO-RS theory takes the important modes of molecular interactions, including electrostatics, hydrogen bonding, and van der Waals interactions into consideration,[43] it is more accurate in coformer ranking than some other methods that only focus on intermolecular hydrogen bonding. Notably, it also reasonably ranks coformers for API solubility improvement. COSMO-RS was recently used to evaluate the cocrystallization propensity of salicylamide and ethenzamide with aromatic carboxylic acids,[44] and guide the screening of dicarboxylic acids for cocrystallization with phenylpiperazine derivatives.[45]

Another virtual cocrystal screening method based on calculated gas phase molecular electrostatic potential surfaces (MEPS) has been developed and validated using data on 18 experimental cocrystal screens from the literature.[18] This method employs surface site interaction points (SSIPs), calculated from the *ab initio* MEPS of the isolated molecule in the gas phase, to identify potential coformers. It was subsequently used to assess the probability of nalidixic acid cocrystal formation, from which 44 coformers with high chance of success were identified and 7 predicted cocrystals were discovered.[46] Similar screening was conducted for discovering novel cocrystals of spironolactone and griseofulvin.[47]

1.2 Cocrystal preparation

Cocrystal preparation methods can be divided into two major categories: solution crystallization and solid-state crystallization.[7] Examples and methodologies for cocrystal production were described by Karimi-Jafari *et al.* in detail.[9] Conventional solvent-mediated methods include slow solvent evaporation, antisolvent addition, supercritical fluid technology, and slurry conversion. Solution crystallization is commonly used in the pharmaceutical industry because it is easily scalable and offers opportunities to control critical crystal attributes (*e.g.*, size, morphology, and polymorphic form).[48] However, the intriguing interplay between the thermodynamics and kinetics of the cocrystallization process often renders the outcome unpredictable and highly method dependent. The phase purity of cocrystals produced by solution cocrystallization is governed by many factors, including the degree of supersaturation, polarity of solvent, and relative solubility of cocrystal formers in the solvent.[49] Failure to obtain cocrystals using a structurally guided approach is sometimes reported,[50–54] making the screening landscape even more serendipitous. For instance, aliphatic

dicarboxylic acids with varying carbon chain lengths are popular coformer candidates with strong hydrogen bond accepting capability. Interestingly, longer chain acids (with carbon number ≥8) usually fail to cocrystallize with a given API by slow evaporation, despite their structural resemblance with other shorter-chain acids. A marked odd-even alternating pattern was also observed such that acids with an odd number of carbon atoms tended to exhibit lower cocrystallization efficiency.[55–57] Wong *et al.* postulated that the discrepancy of cocrystal formability might be partially related to the different glass transition temperatures (T_gs) of the structurally similar dicarboxylic acids, through influencing the overall glass forming ability (GFA) of the binary systems.[58] The odd-numbered diacids have subzero theoretical T_gs compared with their adjacent lower even-numbered diacids, owing to their inability to assume an in-plane orientation of both carboxylic acid groups with respect to the hydrocarbon chain.

The elusiveness of some cocrystals may be ascribed to their inherent thermodynamic instability. To isolate metastable cocrystals, kinetic solvent-mediated approaches, such as rotary evaporation, spray drying, and thermal inkjet printing, are desired since the solvent is removed rapidly so that the molecules can crystallize into a less stable form before they have sufficient time to convert to the most stable crystal form, as predicted by Ostwald's rule of successive stages. Chow and co-workers elucidated the difference in cocrystal formability between the slow and rapid solvent removal techniques, and unveiled the existence of a few elusive cocrystals using rapid solvent removal.[49] Buanz *et al.* assessed the utility of inkjet printing in producing a range of benzoic acid cocrystals.[59] The print head allows production of ultra-fine aerosol (5–15 pL) deposited onto a flat substrate, which is useful for developing personalized-dose orally disintegrating film.[60] Rapid evaporation of the picoliter size droplets in turn favors the fabrication of a metastable cocrystal.

When solvent-mediated methods fail to obtain cocrystals, one can consider solid-state cocrystallization, such as contact formation, grinding, and thermal treatment (*e.g.*, hot melt extrusion, hot-stage microscopy melt interface) to increase the chance for cocrystal synthesis.[7] In these "solvent-free" methods, the complicating effects of solubility and solvent competition are minimized. A successful solid-state reaction highly depends on the intimate contact over a large surface area between coformers.[61] Mechanical stress by grinding facilitates this process by fracturing crystals to promote molecular diffusion through the crystal surfaces. Table 1 summarizes the preparation methods and the types of supramolecular synthons involved in different pharmaceutical cocrystal systems.

2. Cocrystal application in medicine

Without compromising the structural integrity of the API, cocrystallization offers not only solubility and dissolution improvement, but also tuning of mechanical, optical, and organoleptic properties. This opens up a new avenue for patient centric pharmaceutical design aided with an effective manufacturing process. Summarized in the rest of this section are applications of pharmaceutical cocrystallization in modifying some key pharmaceutical properties of an API. The underlying mechanisms and specific role of coformers in modulating the physicochemical properties are also highlighted.

2.1 Solubility

Almost 90% of molecules in the discovery pipeline are poorly water-soluble, leading to minimal oral absorption.[109] Hence, poor aqueous solubility represents a bottleneck restricting the application and commercialization of many drug candidates. Salt formation and amorphization are common strategies for improving the solubility and dissolution of drugs.[110,111] However, their utilities are limited by inapplicability to non-ionic drugs and physical instability issue, respectively. As a promising alternative, cocrystallization can increase solubility through lowering the crystal lattice energy and/or increasing the solvent affinity to different extents, which depends on the molecular rearrangement driven by the coformer.[112] According to Good and Rodriguez-Hornedo, the cocrystal solubility positively correlates with the coformer solubility, of which a coformer with a 10-fold higher solubility can usually lead to a cocrystal that is more soluble than the drug alone.[113] Numerous successful cases of improving the solubility of Biopharmaceutics Classification System (BCS) class II and class IV drugs have been reported in the literature.[64,95,114,115] Particularly, solubility enhancement by cocrystallization is applied extensively to extracted herbal medicines, as many of their clinical efficacies are impaired by the inherently low aqueous solubility.[116] For instance, Ma *et al.* reported improved solubility of apigenin upon cocrystallization with 4,4′-bipyridine.[116] Huang *et al.* demonstrated a 50–100% increase in aqueous solubility of baicalein from pH 3.6 to 6.8 by forming a cocrystal with nicotinamide.[117] Albeit promising, one needs to be aware of the high risk of precipitation of the poorly soluble constituent upon cocrystal dissolution, which negates the solubility advantage of soluble cocrystals. The concept of the "spring and parachute" phenomenon is a good guide when dealing with this risk.[9,118] Sometimes, depression of the solubility of a cocrystal, *e.g.*, by using a "common coformer", can actually improve the dissolution of the cocrystal by avoiding extensive precipitation during dissolution.[119,120]

2.2 Dissolution and bioavailability

Modifying the dissolution rate is the ultimate goal of increasing solubility by cocrystallization. Improving the dissolution rates of poorly soluble APIs enhances bioavailability by allowing a higher concentration of the API for faster absorption. For instance, the ketoconazole–*p*-

Table 1 Design and production of pharmaceutical cocrystals in different therapeutic areas

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
5-Fluorocytosine	Isoniazid	Drug–drug	1 : 1	Slow solvent evaporation with liquid-assisted grinding	Amine–pyridine heterosynthon	Reduced solubility concentration from 0.153 for 5-FC raw and 1.18 for INH raw to 0.119 for the cocrystal	Antimetabolite effects in antifungal treatment	62
5-Fluorouracil	Cinnamic acid	Drug–excipient	1 : 1	Solid-state grinding with slow solvent evaporation	Amide–amide homosynthon, amide–carboxylic acid heterosynthon	Improved anticancer growth inhibiting potential by 67.30% compared to API at 100 μg mL^{-1}	Used as a chemotherapeutic agent against a variety of solid cancers	63
Allopurinol	Piperazine/2,4 -dihydroxybenzoic acid	Drug–excipient	2 : 1/1 : 1	Liquid-assisted grinding and slurry methods	Amine–amine heterosynthon, piperazine nitrogen–piperazine CH heterosynthon	Improved diffusion by 41% at 8 hours for ALP-PIP cocrystal and improved solubility by 50% for the ALP-24DHBZA cocrystal compared to API	Used in the treatment of primary gout, by lowering uric acid levels in the blood and urine and blocking the oxidation process of xanthine and hypoxanthine, and in the treatment of chronic heart failure and tumour lysis syndrome	64
Sulfathiazole	Amantadine hydrochloride	Drug–drug	1 : 1	Liquid-assisted grinding and solvent evaporation	Amine–sulfone heterosynthon, protonated amine–chloride ion–amine charge-assisted heterosynthon	Increased water solubility by 1.83–5.23 times and enhanced penetrability by 2-fold compared to pure sulfathiazole	Antibacterial and antiviral properties	65
Ambrisentan	Syringic acid	Drug–excipient	1 : 1	Mechanochemical grinding	Hydroxy–pyrimidine nitrogen heterosynthon, phenolic hydroxyl–aromatic nitrogen heterosynthon	Increased intrinsic dissolution rate by 1.8-fold and solubility by 4.8 times compared to API	Used in the treatment of pulmonary arterial hypertension	66

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Andrographolide	Salicylic acid	Herb–drug	1 : 1	Slow solvent evaporation	Carboxylic acid–hydroxyl heterosynthon, aromatic ring–hydroxyl heterosynthon, hydroxyl–carbonyl heterosynthon	Improved dissolution rate by 3 times and faster drug release by 2-fold compared to pure andrographolide	Antiviral, anti-inflammatory, anticancer and antimalarial	67
Barbital	Melamine	Drug–excipient	1 : 1	Vial-in-a-vial vapor diffusion crystallization	Amine–carboxyl heterosynthon, amine–amine homosynthon	Modified optical properties with increased relative SGH efficiency by 2 times compared to API	Used in the treatment of anxiety, agitation and insomnia	68
Berberine chloride	Myricetin	Drug–drug	1 : 1	Slurry method	Hydroxyl–chloride anion heterosynthon	Improved hygroscopicity with low moisture adsorption of 1.5% of water up to 95% RH	Used as an antidiarrheal drug with potential in the treatment of cardiovascular diseases and cancer	69
Bumetanide	Caprolactam	Drug–excipient	1 : 1	Liquid-assisted grinding	Carboxylic acid–carboxylic acid homosynthon, amide–amide homosynthon	Improved intrinsic dissolution rate by 1.4 times and improved solubility by 1.7 times compared to API	Diuretic effects used in the treatment of congestive heart failure, hepatic and renal diseases and gentle or mild hypertension	70
Carbamazepine	Saccharin	Drug–excipient	1 : 1	Solution cocrystallization	Sulfone–amino heterosynthon, NH–carbonyl heterosynthon, amino–carbonyl heterosynthon	Comparable solubility with less than 0.05*p* value difference, improved intrinsic dissolution rate by 7.6% and reduced photostability by 10% after 343 hours of irradiation compared to API	Treatment of epilepsy and trigeminal neuralgia	71–73

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Carbamazepine	Nicotinamide	Drug–excipient	1 : 1	Solution cocrystallization	Amide–amide homosynthon	Improvements on intrinsic dissolution rate by 1.8 times compared to API	Treatment of epilepsy and trigeminal neuralgia	72, 74
Chlorothiazide	Carbamazepine	Drug–drug	1 : 2	Slow solvent evaporation	Amide–amide homosynthon, thiadiazine–amide heterosynthon, amide–sulfoxide heterosynthon	Improved thermal stability from 190 °C for carbamazepine to 155.8 °C for the cocrystal and improved dissolution rate by 1.7 times compared to chlorothiazide	Diuretic effects used in the treatment of edema cause by renal dysfunction and in the management of excess fluid linked to congestive heart failure as well as antihypertensive properties	75
Curcumin	Benzenediols/benzenetriols	Herb–excipient	1 : 1	Rapid solvent evaporation *via* rotary evaporation	Phenol–carbonyl heterosynthon, phenol–phenol homosynthon	Simultaneous improvements, compared to API, on hygroscopicity by 7–91%, dissolution rate of CUR–HXQ by 7-fold and tableting behaviour, with four of the five cocrystals, specifically CUR–RES, CUR–HYQ, CUR–HXQ, and CUR–PYR, achieving 2 MPa tensile strength at around 150 MPa	Antioxidant, anti-inflammatory, antimicrobial, antispasmodic, lipid lowering, pro-cognitive, and neuro- and hepato-protective properties	42

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Diacerein	Isonicotinamide/nicotinamide	Drug–excipient	1 : 1	Liquid-assisted grinding	Carboxylic acid–amide heterosynthon, hydroxyl–carbonyl heterosynthon, amide–pyridine heterosynthon, amine–carbonyl heterosynthon, carboxylic–carbonyl heterosynthon	Simultaneous improvements in solubility by ~4 times, dissolution performance by 4.3 times and bioavailability by 2.35 and 3.45 times for ISO and NIC, respectively, compared to API	Anti-osteoarthritic, anti-inflammatory and analgesic properties	40
Diacerein	Theophylline	Drug–drug	1 : 1	Liquid-assisted grinding	Imidazoline–carbonyl 1heterosynthon, carboxylic acid–carbonyl heterosynthon	Increased solubility by 1.8 times, dissolution performance by 2.1 times and bioavailability by 1.69 times compared to diacerein	Anti-osteoarthritic, anti-inflammatory and analgesic properties	40
Diflunisal	Nicotinamide/isonicotinamide	Drug–excipient	2 : 1	Solution crystallization	Carboxylic acid–pyridine heterosynthon, carboxylic acid–amide heterosynthon	Simultaneous improvements on thermal stability, with a melting temperature of 182 °C, and increased dissolution performance, by ~1.5 and 3.0 times for NIC and ISO, respectively, compared to API	Anti-inflammatory properties	76
Diflunisal/diclofenac	Theophylline	Drug–drug	1 : 1	Liquid-assisted grinding	Acid–imidazole heterosynthon, hydroxyl–carboxylic acid heterosynthon	Improved intrinsic dissolution rate by 1.3 times, compared to diclofenac, and improved RH stability with both cocrystals being stable at 100% for up to 2 months	Anti-inflammatory effects with theophylline being used in asthma therapy	77

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Donepezil	1,3-Diiodotetrafluorobenzene	Drug–excipient	1 : 1	Liquid-assisted grinding and solvent evaporation	I···N and I···carbonyl O halogen bond	Increased melting point by 20 °C compared to API	Used to relieve symptoms of Alzheimer's disease	78
Entacapone	Pyrazinamide	Drug–drug	1 : 1	Liquid-assisted grinding	Hydroxyl–pyridine heterosynthon	Improved solubility by 1.5-fold and dissolution rate by 2-fold compared to entacapone	Used in the combined therapy of Parkinson disease with levodopa and carbidopa	79
Ethenzamide	Glutaric acid/malonic acid/maleic acid	Drug–excipient	1 : 1	Neat grinding methods and slow solvent evaporation	Amide–ether oxygen heterosynthon, ether–carboxylic acid heterosynthon, carboxylic acid–carboxylic acid homosynthon	Increased solubility by 1.6 times compared to API	Analgesic and anti-inflammatory effects	80
Ethionamide	Salicylic acid	Drug–drug	1 : 1	Rapid solvent evaporation *via* rotary evaporation	Carboxylic acid–pyridine heterosynthon	Improved dissolution rate with 10 mg L^{-1} more ETH concentration in cocrystal form	Used in the treatment of tuberculosis	81
Famotidine	Theophylline	Drug–drug	1 : 1	Liquid-assisted grinding	Sulfonamide–sulfonamide homosynthon, sulfonamide–carbonyl heterosynthon, imidazole–carbonyl heterosynthon	Improved stability in pH 1.2 as the cocrystal retains original peak position even after 24 h compared to the observed phase changes of form A famotidine within 1 h	Used in the treatment of various kinds of peptic ulcers, acute upper gastrointestinal hemorrhage, gastritis, gastro-esophageal reflux diseases and for protection against the pulmonary target of acid during anesthesia	82

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Febuxostat	Piroxicam	Drug–drug	1 : 1	Liquid-assisted grinding and slow solvent evaporation	Carboxylic acid–pyridine heterosynthon, carboxylic acid–azole heterosynthon, amine–carboxylic acid heterosynthon, carbonyl–methyl heterosynthon, pyridine carbonyl–nitrile heterosynthon	Improved solubility by 1.5-fold in pH 6.8 buffer and 1.24 times in pH 7.4 buffer compared to pure febuxostat and improved dissolution by 2.8-fold compared to pure piroxicam	Used in the treatment of gout	83
Ferulic acid	Isonicotinamide	Drug–excipient	1 : 1	Solid-state grinding, slow solvent evaporation and fast solvent evaporation *via* rotary evaporation	Carboxylic acid–carboxylic acid homosynthon, amide–amide homosynthon, hydroxyl–pyridine heterosynthon	Improved solubility by 3.1-fold compared to API and improved physical stability after 3 months with no significant colour change or phase separation in oleogel	Antioxidant properties used in sunscreen cosmetics and anti-aging products	13
Flufenamic acid	2-Chloro-4-nitrobenzoic acid	Drug–drug	1 : 1	Slow solvent evaporation and liquid-assisted grinding	Carboxylic acid–carboxylic acid homosynthon, aromatic carbon–carboxylic acid heterosynthon	Solubility improvement by 2-fold compared to pure flufenamic acid	Analgesic, anti-inflammatory and antipyretic properties as well as effects in therapy for immunodeficiency diseases as an anti-viral and anti-cancer agent	84
Flufenamic acid	Ethenzamide	Drug–drug	1 : 1	Slow solvent evaporation and liquid-assisted grinding	Carboxylic acid–amide heterosynthon, phenyl–carboxylic acid heterosynthon, phenyl–ketone heterosynthon	Solubility improvement by 5-fold in 0.1 N HCl solution compared to pure flufenamic acid	Analgesic, anti-inflammatory and antipyretic properties	84

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Flufenamic acid	Theophylline	Drug–drug	1 : 1	Slow solvent evaporation	Imidazole–carbonyl heterosynthon, carboxylic acid–imidazole heterosynthon	Improved hygroscopicity with a low adsorption rate (<2%) over a wide humidity range and improved solubility by 2 times compared to pure flufenamic acid	Analgesic, anti-inflammatory and antipyretic properties with theophylline being used in the treatment of respiratory diseases	85
Fluoxetine hydrochloride	Fumaric acid/benzoic acid/succinic acid	Drug–excipient	2 : 1	Slow solvent evaporation	Protonated amine–carbonyl heterosynthon, protonated amine–chloride ion heterosynthon, carboxylic acid–chloride ion heterosynthon	Increased solubility by 30% compared to API	Antidepressant, anti-anxiety, antiobsessional and anti-bulimic activity	86
Furosemide	*p*-Aminobenzoic acid	Drug–excipient	1 : 1	Slow solvent evaporation with neat and liquid-assisted grinding	Carboxylic acid–carboxylic acid homosynthon, sulfone–amine heterosynthon	Increased dissolution rate by 2 times compared to API	Loop diuretic drug used in the treatment of hypertension and edemas from cardiac, renal and hepatic failure	87, 88
Furosemide	Isonicotinamide	Drug–excipient	1 : 1	Slow solvent evaporation with neat and liquid-assisted grinding	Ketone–amine heterosynthon, carboxylic acid–aromatic nitrogen heterosynthon, amine–ketone heterosynthon	Increased solubility by 7.2-fold and intrinsic dissolution rate by a factor of 2.3 compared to API	Loop diuretic drug used in the treatment of hypertension and edemas from cardiac, renal and hepatic failure	87
Hydrochlorothiazide	Pyrazinamide	Drug–drug	1 : 1	Reaction crystallization	Sulfonamide–amino heterosynthon, amide–pyridyl nitrogen heterosynthon, carbonyl–amide, heterosynthon	Reduced melting point by 75 °C and improved solubility and dissolution performances by 1.4 times compared to hydrochlorothiazide	Diuretic effects used in the treatment of hypertension and edemas	89

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Ibuprofen/flurbiprofen	Nicotinamide	Drug–excipient	1 : 1	Rapid solvent evaporation *via* rotary evaporation	Carboxylic acid–pyridine heterosynthon	Improvements on tableting behavior, specifically an increased tablet tensile strength with increasing compaction pressure up to 150 MPa; reduced hygroscopicity by 2.5 and 4 fold for IBU and FLU, respectively; increased dissolution rates by ~3 and ~5 fold for IBU and FLU, respectively, all compared to API	Anti-inflammatory, antipyretic, and analgesic properties	6
Indomethacin	Saccharin	Drug–excipient	1 : 1	Slow solvent evaporation with liquid-assisted grinding methods	Carboxylic acid–imide heterosynthon	Simultaneous improvements on hygroscopicity by more than 0.05% and dissolution performance by more than 50 times compared to API	Anti-inflammatory, antipyretic, and analgesic properties	90
Isoniazid	Resveratrol	Drug–herb	1 : 1	Reaction crystallization method	Hydroxyl–pyridine heterosynthon, carbonyl–hydroxyl heterosynthon, amine–hydroxyl heterosynthon	Reduced permeability by 86% compared to API	Used in the treatment of cutaneous tuberculosis	91
Itraconazole	Suberic acid	Drug–excipient	1 : 1	Rapid solvent evaporation *via* rotary evaporation and spray drying	Triazole–carboxylic acid heterosynthon	Improvements on dissolution performance by 39 times compared to API	Indicated for blastomycosis, histoplasmosis, aspergillosis, and onychomycosis	92

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Lamotrigine	Phenobarbital	Drug–drug	1 : 1	Slow solvent evaporation with liquid-assisted grinding	Amine–carbonyl heterosynthon, pyridine–amine heterosynthon	Increased melting point by 45 °C and 87 °C and reduced intrinsic dissolution rate by 75% and 94.6%, for pure lamotrigine and phenobarbital, respectively	Indicated for primary generalized tonic–clonic seizures and used in the treatment of epilepsy and neonatal seizures	93
Levofloxacin	Metacetamol	Drug–drug	1 : 1	Grinding and heating approach	Hydroxyl–*N*-methylpiperazine heterosynthon, hydroxyl–amine heterosynthon, amine–carboxylic acid heterosynthon	Similar dissolution profile to hydrated levofloxacin, improved hygroscopicity, with 0.3% water uptake at 95% RH and improved physical stability of the cocrystal for 4 weeks under all conditions	Antibacterial agent with antipyretic analgesic effects	94
Meloxicam	Aspirin	Drug–drug	1 : 1	Solution, slurry and liquid-assisted grinding	Azole–carboxylic acid heterosynthon, azole–alcohol heterosynthon	Improved bioavailability by 12-fold compared to pure meloxicam	Indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis	95
Naproxen	Nicotinamide	Drug–excipient	2 : 1	Liquid-assisted grinding	Carboxylic acid–amide heterosynthon, carboxylic acid–pyridine heterosynthon	Improved intrinsic dissolution rate by 2.8-fold compared to API; prevented hydration of naproxen to dihydrate and tetrahydrate with less than 1% water absorbance even at high RH values	Anti-inflammatory and analgesic effects in joints and muscles used to treat diseases of joints	96

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Nevirapine	Salicylic acid	Drug–excipient	2 : 1	Slow solvent evaporation	Carboxylic acid–pyridine heterosynthon	Improved solubility by 1.1-fold compared to pure nevirapine	Antiretroviral effects used in the therapy of HIV-1 infection and AIDS	97
Nifedipine	Isonicotinamide	Drug–excipient	1 : 1	Slow solvent evaporation	Benzene–pyridine heterosynthon	Reduced melting point by 50–60 °C compared to API and improved photostability with no obvious change in assay value (98%) after 10 hours of exposure	Used in the treatment of hypertension and angina	98
Nitrofurantoin	Nitrofurantoin-4-hydroxybenzoic acid	Drug–excipient	1 : 1	Solid-state grinding	Imide–phenol heterosynthon, carboxylic acid–carboxylic acid homosynthon	Improved stability with no changes under all RH conditions and improved photo-stability with 11% less degradation after 168 hours of UV irradiation compared to API	Antibacterial effects used in the treatment of urinary tract infections	99
Oxaliplatin	Naringenin	Drug–herb	1 : 1	Slow solvent evaporation and grind-evaporation methods	Carbonyl–phenol heterosynthon, carbonyl–hydroxyl heterosynthon, carbonyl–amine heterosynthon	Reduced solubility by 7-fold compared to API and delayed hydrolysis, with 93.75% of residual OXA after 8 hours	Anticancer agent used in the treatment for colorectal, gastric and pancreatic cancer	100
Paracetamol	Trimethylglycine	Drug–nutraceutical	1 : 1	Solid state grinding	Hydroxyl–carbonyl heterosynthon, carbonyl–amide heterosynthon	Simultaneous improvements on hardness, dissolution performance, by 1.2 times compared to API, and organoleptic properties through masking of the bitter taste	Antipyretic effects	101

Table 1 *(continued)*

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Piroxicam	Clonixin	Drug–drug	1 : 1	Slurry method and solvent evaporation	Carboxylic acid–deprotonated hydroxyl heterosynthon, protonated pyridine–amide carbonyl heterosynthon	Unchanged cocrystal form and colour within one month indicating improved moisture stability	Used to relieve the symptoms of painful inflammatory conditions	102
Pyrazinamide	1,4-Diiodotetrafluorobenzene	Drug–excipient	2 : 1, 1 : 1	Liquid-assisted grinding and solvent evaporation	I⋯pyrazinyl N halogen bonding and amide–carbonyl heterosynthon	Reduced melting point by 24 °C compared to API	Used in the treatment of tuberculosis	103
Sildenafil	Acetyl salicylic acid	Drug–drug	1 : 1	Solution cocrystallization	Carboxyl–piperazine heterosynthon	Improved intrinsic dissolution rate by 75% compared to pure sildenafil	PDE5 inhibitor used in the treatment of angina, hypertension, congestive heart failure, and atherosclerosis	104
Sulfamethizole	Adipic acid	Drug–excipient	2 : 1	Liquid-assisted grinding	Amine–carboxylic acid heterosynthon, amine–sulfone heterosynthon	Reduced melting point by 32 °C and reduced intrinsic dissolution rate by 0.61 times compared to API	Sulfonamide class antibiotic that competitively inhibits folate synthesis in microorganisms	105
Tegafur	Isonicotinamide	Drug–excipient	1 : 1	Solution crystallization and solid-state grinding	Amide–imide heterosynthon, amide–amide homosynthon	Improved hygroscopicity through negligible (<1%) moisture sorption and improved solubility by 2.3 times compared to API	Used in the treatment of cancerous tumors and in various malignancies, particularly gastrointestinal, bowel and breast cancers	106
Telmisartan	Atenolol	Drug–drug	2 : 1	Liquid assisted grinding	Carboxyl–amide heterosynthon	Increased solubility by 2-fold compared to pure telmisartan	Angiotensin II receptor blocker, with atenolol being used in the treatment of cardiovascular disease and hypertension	107

Table 1 (continued)

Drug	Coformer	Classification	Stoichiometric ratio	Preparation method	Supramolecular synthon	Change of properties	Therapeutic area	Ref.
Tenoxicam	Salicylic, succinic and glycolic acid	Drug–excipient	1:1	Liquid-assisted grinding	Carboxylic acid–hydroxyl heterosynthon, carboxylic acid–deprotonated hydroxyl heterosynthon, deprotonated hydroxyl–amide heterosynthon, protonated pyridine–amide heterosynthon	Similar or reduced dissolution performance by 29–91% compared to API	Anti-inflammatory effects	108

aminobenzoic acid cocrystal exhibited 10-fold and 6.7-fold higher aqueous solubility and bioavailability than ketoconazole, respectively.[121] Huang *et al.* prepared a baicalein–nicotinamide cocrystal with a 2.46-fold increase in dissolution performance in pH 6.8 buffer, resulting in a 2.49-fold and 2.80-fold higher peak plasma concentration and area under the curve in rats.[117]

Relative to dissolution enhancement using soluble cocrystals, the use of a less soluble cocrystal for extended release of a drug is less frequently reported. The extended release form demonstrates various advantages in pharmaceutical applications, including lowering dosing frequency, improving patient compliance and reducing side effects.[122] Xuan *et al.* reported the successful synthesis of an extended release isoniazid cocrystal by cocrystallizing hydrophilic isoniazid with the hydrophobic curcumin.[123] Without using polymers to attain extended release, isoniazid slowly dissolved from the cocrystal up to 48 h and 24 h in pH 1.2 and pH 6.8 phosphate buffers, respectively, in contrast to the immediate release of isoniazid within 15 min. The extended release behavior was due to the blockage of solvation sites of isoniazid by curcumin, and the recrystallization of curcumin form III onto the surface of undissolved cocrystals. Xiao *et al.* developed three extended release cocrystals of the hyperthyroidism drug propylthiouracil with nutraceuticals (cinnamic acid, ellagic acid, and kaempferol) to reduce its release rates and hepatotoxicity.[124] The propylthiouracil–kaempferol cocrystal showed the lowest intrinsic dissolution rate of 12.0% and 20.8% of that of propylthiouracil when dissolving in pH 1.2 and pH 6.8 buffers. The calculation model indicates that the enhanced lattice energies and hydrophobic interactions could give rise to lower solubility and a sustained release effect. The order of the dissolution rates of these three cocrystals was consistent with the order of the hydrophobicity/hydrophilicity proportion within the cocrystals. For instance, the propylthiouracil–kaempferol cocrystal with the lowest intrinsic dissolution rate possesses the highest hydrophobic proportion.

2.3 Hygroscopicity

The susceptibility of a drug to hydration can have detrimental effects on solubility, dissolution performance, manufacturability, and physical stability of a drug substance. Reduction in hygroscopicity is, therefore, vital to enable a successful dosage form development. Cocrystallization of non-hygroscopic curcumin with benzenediols or benzenetriols can depress their moisture sorption tendency.[42,49] Particularly, it effectively alleviated the phase transformation of phloroglucinol from an anhydrate into a dihydrate (Fig. 2).[49] The role of coformers in reducing hygroscopicity can be related to the crystal lattice strengthening effect and hydrogen bond occupancy for water sorption.[49] A stronger cocrystal lattice, reflected by a higher molar enthalpy of fusion relative to the coformers, renders

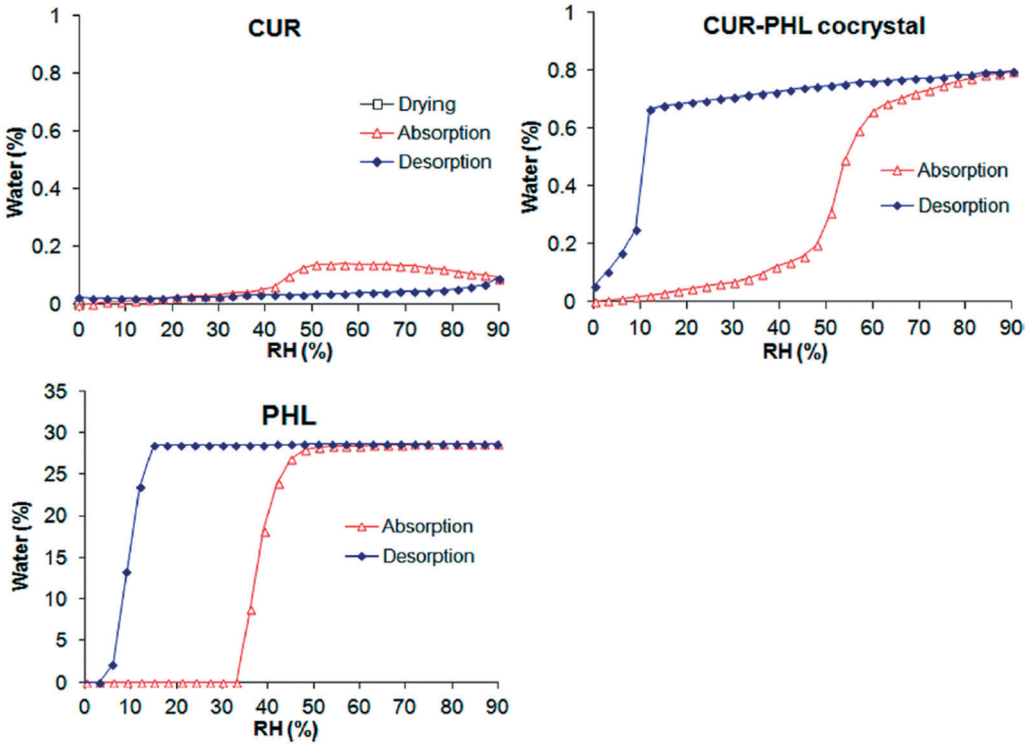

Fig. 2 DVS isotherms of curcumin, phloroglucinol, and the cocrystal (reprinted with permission from ref. 49. Copyright (2014) American Chemical Society).

them less accessible to water. The phenolic groups present on the surface of crystals of benzenediols and benzenetriols freely interact with water molecules in the surrounding environment, contributing to their hygroscopic nature. Upon cocrystallization, the phenolic groups are predominantly engaged in phenol–phenol and/or phenol–carbonyl intermolecular hydrogen bonding interaction with curcumin. This makes them less accessible for interacting with water *via* O–H···O hydrogen bonds, which reduces their hygroscopicity.[49] Similarly, a reduced moisture sorption of nicotinamide by 2.5–4-fold has been reported for the ibuprofen–nicotinamide and flurbiprofen–nicotinamide cocrystal systems, through forming N···H–O hydrogen bonds between the pyridine group of nicotinamide and carboxylic acid of profen.[6] Improved hygroscopicity was also demonstrated in indomethacin–saccharin, *s*-oxiracetam–gallic acid, and piroxicam–clonixin cocrystal systems.[90,102,125,126]

2.4 Mechanical properties

Mechanical properties (*e.g.*, tabletability, flowability, and punch sticking properties) are important criteria to consider when assessing the manufacturability of a drug substance. Approximately 80% of the current drugs are not suitable for direct compression.[127] Conventionally, excipients are needed to improve the mechanical properties.[127] Cocrystallization has emerged as a useful strategy to overcome the poor compressibility problem of drugs, such as paracetamol, curcumin, baicalein, and resveratrol.[5,42,128,129] Coformers may influence the mechanical properties through altering the supramolecular features of the parent drug, such as slip planes, surface topologies, intermolecular interactions, and interparticulate bonding strength.[130–132] Liu *et al.* demonstrated that the deficient tabletability of α form baicalein can be solved by cocrystallizing with coformers possessing high (nicotinamide), medium (caffeine), and even poor tabletability (isoniazid) (Fig. 3).[128] An energy framework analysis suggested that the superior tabletability, irrespective of the coformer characteristics, was correlated with the unique cocrystal structure rendering high plasticity.[128] While molecular crystals are generally regarded as being brittle, many elastically flexible molecular crystals have been reported. For instance, an elastic and bendable methanol solvate of the cocrystal between caffeine and 4-chloro-3-nitrobenzoic acid showed excellent shape recovery after bending at room temperature and −100 °C.[133] The interlocked host structure with weak interactions in the crystal, and the presence of mobile solvent channels were considered to contribute to the high flexibility of the cocrystal. Wang *et al.* showed that cocrystallization of celecoxib with L-proline can significantly mitigate the propensity of punch sticking,[134] a prevalent problem during commercial tablet manufacturing. Unwanted adherence of powder mass onto the punch roughens the tablet surface and causes inconsistent drug content.[135] The lower punch sticking propensity of the celecoxib cocrystal can be ascribed to reduced plasticity through deactivating slip planes and less exposed electronegative functional groups to the punch tip during compression.[134]

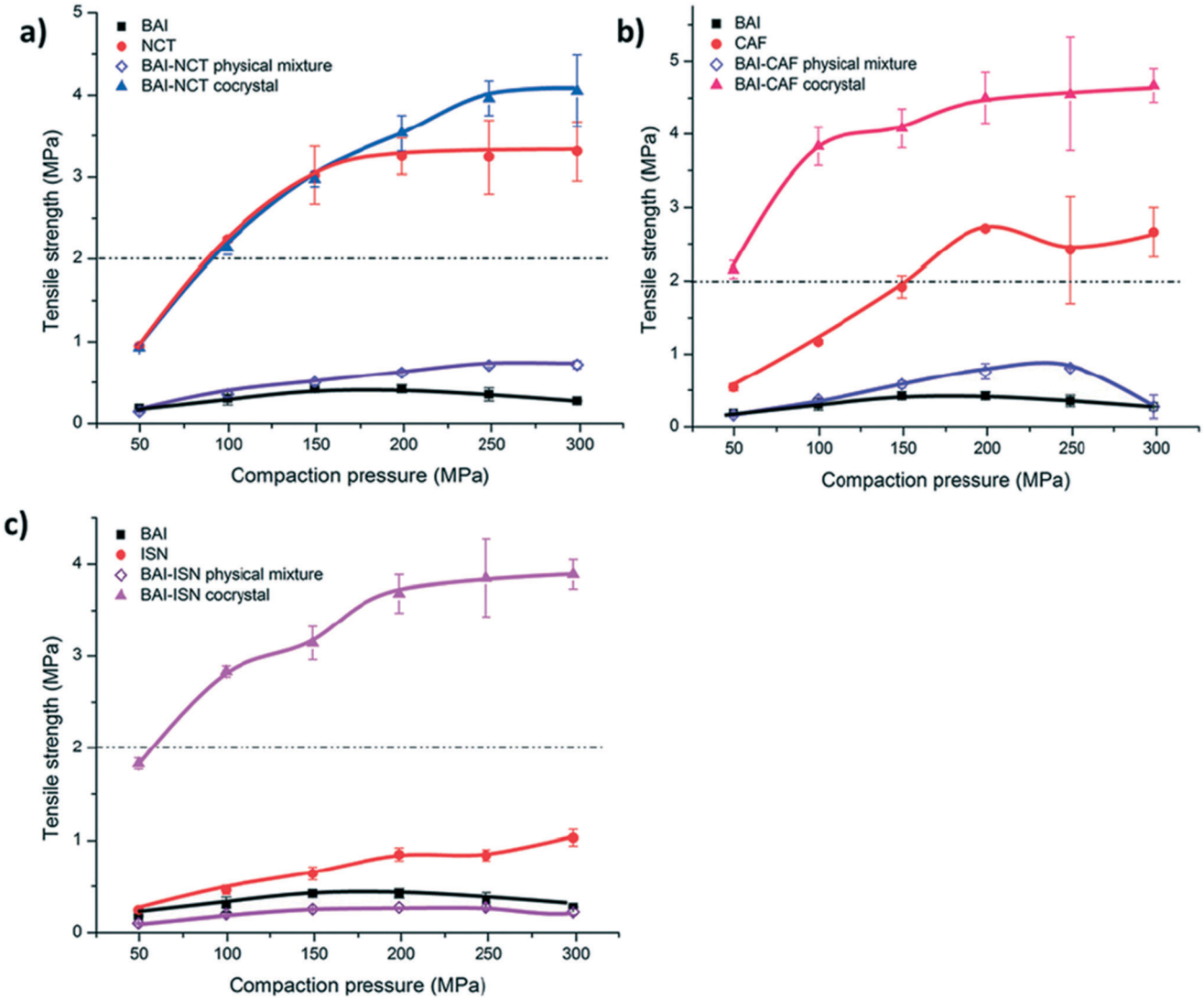

Fig. 3 An example of tabletability of (a) baicalein–nicotinamide (BAI–NCT), (b) baicalein–caffeine (BAI–CAF), and (c) baicalein–isoniazid (BAI–ISN) cocrystals (reprinted with permission from ref. 126. Copyright (2018) The Royal Society of Chemistry).

2.5 Photostability

Significant photo-instability not only diminishes the drug stability and efficacy, but also potentially causes serious photoallergic reaction by the photodegradation products.[136] Cocrystallization bears the potential to modify the photostability of a drug by introducing a coformer which can alter the molecular packing in the crystal lattice and hence, prevent the photoredox reaction,[94] photodimerization,[137,138] and photoisomerization[139] upon exposure to light. For instance, Shinozaki *et al.* synthesized a levofloxacin–metacetamol cocrystal, which exhibited improved photostability and less severe discoloration in solid, solution and suspension states with respect to levofloxacin.[94] The advantage can be ascribed to the hydrogen bond formation between the hydroxyl group of metacetamol and the *N*-methylpiperazine group of levofloxacin, which displaced the electron in the N–H σ-bond toward the nitrogen and prevented the oxidation of the *N*-methylpiperazine moiety involved in photodegradation.[94] Putra *et al.* improved the photostability of epalrestat by preventing its *E*,*Z* to *Z*,*Z* isomerization through cocrystallization with betaine, which resulted in a strong O···O hydrogen bonded network and reduced the reaction cavity size.[139] Apart from the choice of coformers, it must be stressed that whether cocrystallization could offer photoprotection is associated with the cocrystal polymorphic form. Yutani *et al.* indicated that a form II carbamazepine–saccharin cocrystal facilitated the photodegradation of carbamazepine, which contrasts the photoprotective effect of the form I carbamazepine–saccharin cocrystal, plausibly due to the increase in molecular mobility.[73] Likewise, the form II nifedipine–isonicotinamide cocrystal exhibited a deteriorated photostability with only 80% nifedipine remaining under identical stability conditions.[98] In contrast, no obvious change was observed for the form I nifedipine–isonicotinamide cocrystal (98%)

possibly due to a shorter bond length than form II, *i.e.*, between the O1 atom on the nitro group and the H4 atom on the dihydrogen pyridine ring.[98]

2.6 Luminescence properties

The luminescence properties of an API create an opportunity for the development of fluorescence-based biosensors, as well as bioanalytical and diagnostic tools.[140] Introduction of coformers can change the geometric arrangement of the functional chromophores of the drug in the form of a cocrystal, leading to modulated fluorescence.[141,142] Early studies by Yan *et al.* demonstrated the feasibility of modifying the luminescent behaviors of organic materials by cocrystallization.[142] They reported that a stilbene cocrystal with a series of aromatic coformers showed a remarkably different UV/vis absorption and luminescence emission.[142] The cocrystals showed multi-color emission from blue through green to yellow as well as strong two-photon luminescence, due to the geometric arrangement change of the 1,4-bis-*p*-cyanostyrylbenzene chromophore in the cocrystal. Moreover, differential fluorescence properties, *e.g.*, color, and emission wavelength, were exhibited by different polymorphic forms of cocrystals.[143,144]

Recently, such application has been extended to pharmaceutical crystals. Huang *et al.* tuned the photoluminescence of a dietary flavonoid phloretin through cocrystallization.[145] Under a 365 nm UV lamp, the phloretin–nicotinamide cocrystal exhibits strong yellowish-green fluorescence, but no fluorescence was observed in phloretin and the phloretin–isonicotinamide cocrystal. The zigzag packing in the phloretin–nicotinamide cocrystal resulted in a weaker π–π interaction, which promotes an intense fluorescence emission, whereas the planar structure of the phloretin–isonicotinamide cocrystal did not favor luminescence due to a tight π–π interaction.[145] These findings imply that cocrystallization can potentially substitute the traditional methods, *e.g.*, using fluorescent dyes as labels,[146] to detect the cellular uptake of organic drugs.

2.7 Organoleptic properties

The organoleptic properties of drug products can have an impact on patient compliance, especially for pediatric and geriatric populations. Apart from achieving a taste-masking purpose by coupling with sugar-based coformers,[101,147–149] the appearance of a drug product, *i.e.*, color, can also be modified by cocrystallization. This offers a better alternative to using synthetic pigments, which may cause toxicity. The fine tuning of color could be ascribed to different π stacking patterns, hydrogen bonding and charge-transfer interactions after cocrystallization with coformers possessing different chemical and photophysical properties. For example, Zhu *et al.* showed that the color of vitamin K3 evolved from yellow to orange by forming cocrystals with naphthoic acids and sulfamerazine.[137] This involved charge-transfer transitions occurring from the highest occupied molecular orbital of the electron donor (coformers) to the lowest unoccupied molecular orbital of the electron acceptor (quinone ring of vitamin K3).[137] Interestingly, Sangtani *et al.* reported a color cocrystal polymorphism of furosemide with 4,4′-bipyridine, where the individual components are colorless while light yellow and orange color developed in form II and form III cocrystals, respectively.[150] Calculation by density functional theory further suggested a decrease in the gap between the highest occupied molecular and lowest unoccupied molecular orbital for form III cocrystals compared to form II crystals. Significant color change was also observed in isoniazid–curcumin (Fig. 4),[123] metronidazole–pyrogallol,[151] and a series of emodin and 4-aminoazobenzene-based cocrystals.[152,153]

3. Challenges in translational development of cocrystals

The past decade witnessed significant strides being made in the exploration of pharmaceutical cocrystals. Many cocrystal-based patents or patent applications have been published. Several cocrystal products have gained regulatory approval (*e.g.*, Steglatro®, Lexapro®, Entresto®, and Suglat®) and more in clinical trial phases (ClinicalTrials.gov identifier: NCT03108482, NCT02723201).[154–158] With an exponential increase of cocrystal structure reported in the Cambridge Structural Database, it is surprising that the number of marketable cocrystal drug products is still lagging behind those based on other novel crystal engineering techniques, such as nanotechnology. Challenges pertaining to the quality control, manufacturing, and regulation of cocrystal drug products still exist during development and scale-up. This section sheds light on a few key issues constituting the translational gap for cocrystal drug products (Fig. 5).

3.1 Industrial scale-up of cocrystal production

Attaining efficient and effective cocrystal production at larger scales without compromising product quality is an essential goal in the industry. The operation of cocrystallization processes is traditionally based on the batch production mode, which is associated with high energy requirements, low efficiency, long throughput time, and non-uniform mixing, due to unpredictable processing variables.[159] Hence, pharmaceutical manufacturers have started to shift into continuous cocrystallization in order to meet changing market demands and better fit the regulatory frameworks, by providing a more flexible process control and consistent product quality. The two main categories of cocrystal screening methods, *i.e.*, mechanochemical and solution-based cocrystallization, possess different limitations upon scaled-up production. Solid-state grinding using a mortar and pestle and ball milling are less practical to scale up for manufacturing multi-kilo or tons of products.[160] Within solution-based methods, antisolvent, slurry and cooling cocrystallization are demonstrated as most suitable for

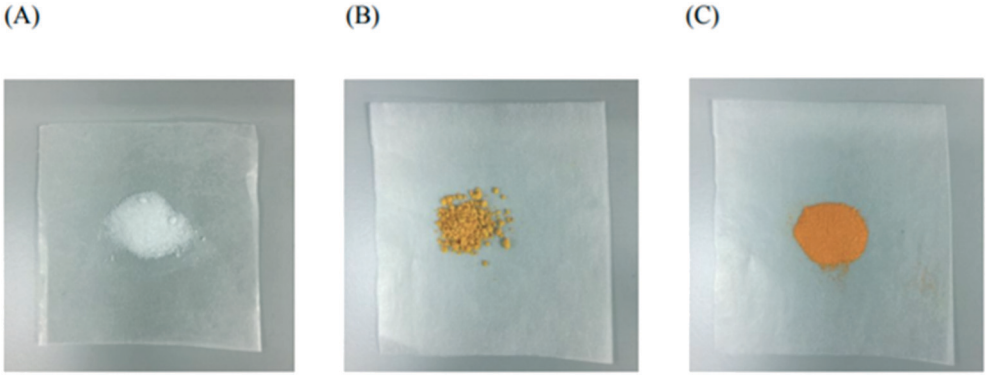

Fig. 4 Color change of (A) isoniazid and (B) curcumin compared with (C) isoniazid–curcumin cocrystal (reprinted with permission from ref. 121. Copyright (2020) American Chemical Society).

scaled-up production, compared with solvent evaporation by which the purity of crystal forms produced is largely impacted by the incongruent coformer solubility during the long processing time.[48] One should therefore consider constructing phase solubility diagrams (PSDs) and ternary phase diagrams (TPDs) to guide the selection of processing parameters by mapping out the critical region where the cocrystal exists as the solely stable solid phase.[161,162] Notably, the unique opportunity offered by hot melt extrusion (HME) and resonant acoustic mixing (RAM) in industrial cocrystal production has been gaining more attention in recent years.[163] HME was used to continuously produce large batches of caffeine–oxalic acid, carbamazepine–saccharin (100-gram scale), theophylline–nicotinamide cocrystals, *etc.*[164,165] RAM with optimized parameters allowed the mass production of an 80-gram theophylline–oxalic acid cocrystal with a net yield of 94%.[166] These simple, rapid, and environmentally friendly techniques are anticipated to become more popular tools for high quality cocrystal production in the industry in the future.

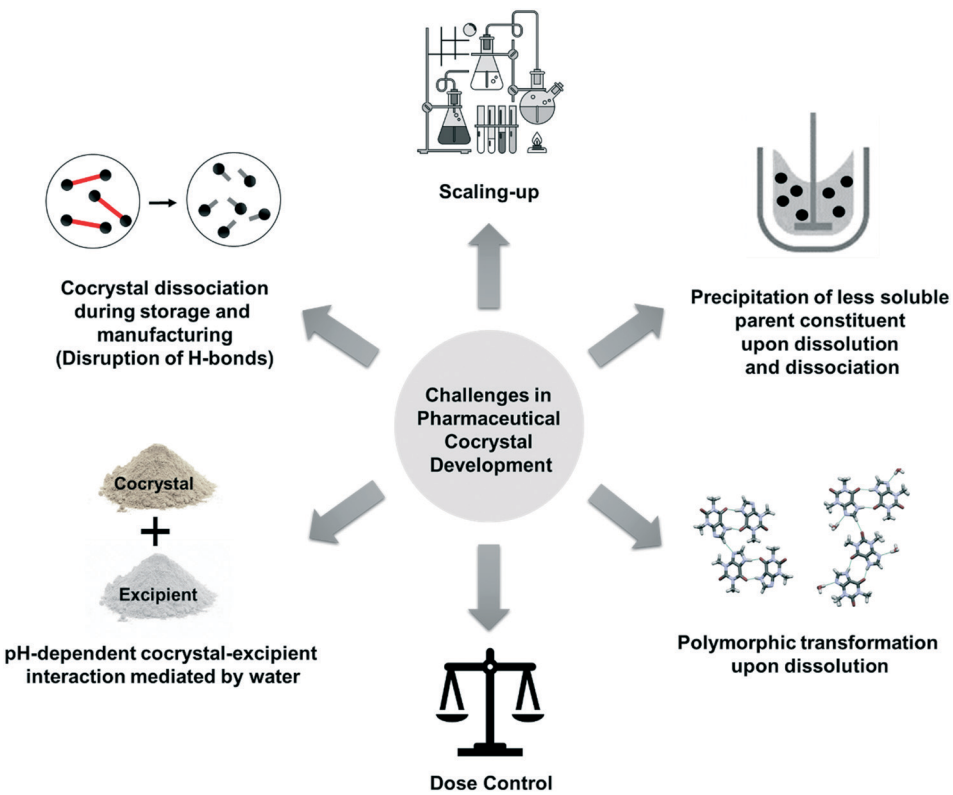

Fig. 5 A schematic diagram depicting the challenges of pharmaceutical cocrystal product development.

3.2 Inflexible dosing regimen of drug–drug cocrystals

In addition to the commonly discussed scale-up issue, the utility of drug–drug cocrystals in medicine is restricted by inflexible dosage. The stoichiometric ratio of the cocrystal is generally fixed as 1:1, 1:2, or 2:1. The dose of cocrystal formers thus may not be in agreement with its recommended therapeutic dose for specific indications.[167] An excessive amount of either cocrystal formers appears inevitable and may associate with toxicity. But it is worth noting that cocrystallization imparts potential enhancement in bioavailability.[40,95] Dose reduction is thus possible in the cocrystal product for achieving an equivalent therapeutic efficacy to the conventional formulation. An adequate dose-finding study would be of the utmost importance during clinical development of a new cocrystal drug product.

3.3 Cocrystal dissociation in the solid state

In addition to the commonly discussed scale-up issue and inflexible dosing regimen, the utility of drug–drug cocrystals in medicine is restricted by spontaneous cocrystal dissociation. A cocrystal must stay intact during the product manufacturing and storage, particularly be resistant to high humidity and high temperature conditions. Cocrystal dissociation into the individual constituents negates the beneficial properties brought by cocrystallization. Cocrystal dissociation at high humidity is postulated to be intimately linked to a large solubility difference in the coformers, especially when these molecules can form hydrates.[168,169] Importantly, the fundamental cocrystal research efforts centered on improving the aqueous solubility profile of hydrophobic compounds with the aid of a hydrophilic coformer. The large solubility difference thus renders cocrystal dissociation a possible risk.[169]

The dissociation can occur under relatively mild conditions, exemplified by the pyrazine–phthalic acid cocrystal, which dissociated completely in one day due to the loss of pyrazine.[170] Trask *et al.* reported that the dicarboxylic acid cocrystals of caffeine and theophylline dissociated within 7 days at 98% relative humidity, leading to recrystallization of the cocrystal formers separately.[126,171] The potential driving force for cocrystal dissociation at high humidity was further discussed by Eddleston *et al.* using ternary phase diagrams.[169] Moreover, Thakuria *et al.* depicted that the form I caffeine–glutaric acid cocrystal polymorph transformed to form II at high humidity, followed by deliquescence and recrystallization of caffeine hydrate.[172] The cocrystal can also be susceptible to dissociation upon heating. A theophylline–caffeine cocrystal underwent a solid-state dissociation when heated to a temperature below the melting point, whereby caffeine and theophylline molecules spontaneously separated and recrystallized as distinct crystalline entities.[173] Even partial cocrystal dissociation can be a problem leading to batch rejection in pharmaceutical manufacturing. More future efforts are warranted to mitigate the risk of unintended cocrystal dissociation under stressed conditions.

3.4 Cocrystal dissociation and transformation in solution

Most existing cocrystal studies focused on improving the dissolution rates of less soluble APIs, but such improvement may result in the rapid recrystallization of the poorly soluble APIs during dissolution.[120] In other words, a soluble cocrystal may not necessarily fully realize its potential advantages of high solubility. This kind of phenomenon is referred to as solution-mediated phase transformation (SMPT) of a cocrystal. When the solubility of a cocrystal is higher than its parent API, it is possible to achieve the supersaturation status, which may further lead to the recrystallization of the parent API. Commonly, the recrystallized solid phase is either the parent constituents or their hydrates.[42,115,174,175]

Qiao *et al.* reported the high degree of supersaturation (around 140) at the surface of the carbamazepine–nicotinamide cocrystal, leading to rapid recrystallization of carbamazepine dihydrate in the diffusion layer, which coated the cocrystal so that no improvement of the dissolution rate was shown.[175] Similarly, Chow *et al.* explained the lack of dissolution improvement of the curcumin–phloroglucinol cocrystal by the immediate transformation of the curcumin cocrystal to curcumin form I on the surface upon contact with the dissolution medium, which was indicated by the color change from dark red to bright yellow.[49] Wong *et al.* prepared five curcumin cocrystals for intrinsic dissolution rate measurement, and confirmed the recrystallization of curcumin form I from both the color change and PXRD after contact with the dissolution medium.[42] The phase transformation was completed within a few seconds due to the high driving force, high degree of supersaturation, brought about by the high solubility of the cocrystal. Omori *et al.* used the carbamazepine–glutaric acid cocrystal to investigate whether the SMPT occur in the bulk phase or at the particle surface and found that >95% of cocrystals were transformed to carbamazepine dihydrate within 3 min by particle surface-SMPT.[176] The real-time polarized light microscopy data implied that particle surface-SMPT occurred immediately upon contact with the dissolution medium. In order to control the cocrystal dissolution, supersaturation and precipitation, Huang *et al.* demonstrated a quantitative method for additive selection.[177] The experimental results with the indomethacin–saccharin cocrystal illustrated that a cocrystal solubility advantage (SA) value of 10 could reach and sustain supersaturation to prevent the occurrence of SMPT.[177]

Interestingly, metastable polymorphic forms could also be obtained through cocrystal dissociation and recrystallization during dissolution. Xuan *et al.* demonstrated that the dissolution of a curcumin–isoniazid cocrystal in pH 1.2 and pH 6.8 phosphate buffers could yield metastable curcumin form III upon cocrystal dissociation.[123] One possible reason is that the curcumin cocrystal could achieve a very high

supersaturation level when dissolved in phosphate buffers relative to the low solubility of curcumin. The fast crystallization kinetics led to the precipitation of the metastable curcumin form III in accordance with Ostwald's rule of stages. Due to different physicochemical properties between different crystal forms, it is crucial to analyze and control the dissolution process of pharmaceutical cocrystals, and the accidental precipitation of different polymorphs may influence the bioavailability of a drug product. Addition of polymeric nucleation inhibitors, such as hydroxypropyl methylcellulose acetate succinate, to the formulation could retard nucleation and crystal growth and prevent unwanted API precipitation during dissolution.[120]

Due to the limitations of current technologies, cocrystal dissociation and transformation in the solution-state are clearly less discovered, which represents one of the major uncertainties hindering cocrystal translational development. Only a few technologies, like real-time Raman spectroscopy and polarized light microscopy, could be utilized to get some supporting information. Efforts in exploring more versatile and robust experimental approaches to elucidate the underlying mechanism and phenomena of cocrystals in the solution-state are needed to facilitate pharmaceutical cocrystal applications in the future.

3.5 Cocrystal–excipient interaction

Excipients, such as fillers and binders, are typically blended with the API to improve the performance of the final cocrystal product. Excipients possessing hydrogen bond donor or acceptor functionalities nonetheless can compete with the coformer for the hydrogen bonding sites of the API.[178,179] To develop robust cocrystal-based formulations, the potential cocrystal–excipient interactions must not be neglected. Coformers show a specific role in determining solid-state cocrystal stability in the presence of excipients.[180] The stability was shown to be linked to the coformer's ability to ionize in response to the microenvironment created by the excipient, such that acidic, basic, and neutral coformers can drive different outcomes.

Walsh *et al.* proved the feasibility of producing an ibuprofen cocrystal with a basic coformer isonicotinamide in the presence of an excipient *via* spray drying and hot melt extrusion.[181] Similarly, Aljohani *et al.* showed that a total of 9 chlorothiazide cocrystals remained unchanged *in situ* during milling in the presence of polyvinylpyrrolidone, microcrystalline cellulose, *etc.*[178] Li *et al.* demonstrated that the addition of an inert excipient Soluplus can improve the cocrystallization efficiency of ibuprofen–nicotinamide *via* hot melt extrusion by enabling a low processing temperature.[182] It can further enhance the interaction between the API and coformer, leading to better mechanical properties (*i.e.*, tabletability, compactibility and compressibility) compared with the pure ibuprofen–nicotinamide cocrystal.[183]

Nonetheless, these observations appear invalid in a cocrystal with an acidic coformer. Duggirala *et al.* highlighted that the caffeine–oxalic acid cocrystal is stable under high humidity, whereas it undergoes water-mediated dissociation in the presence of numerous ionizable excipients (*e.g.*, magnesium stearate) during storage.[184] It is attributed to the proton transfer from oxalic acid to the anionic group of the excipient. Milling of the caffeine–oxalic acid cocrystal with dicalcium phosphate anhydrate can trigger measurable lattice disorder and high water sorption propensity for the cocrystal, which further accelerated the dissociation at the interface of the cocrystal and excipient particles possessing lattice defects.[185] Similar observations have been seen in the theophylline–glutaric acid and ertugliflozin–L-pyroglutamic acid (Steglatro®) cocrystals. These findings substantiate the tendency of basic excipients to induce dissociation of cocrystals containing acidic coformers during manufacturing and storage, while acidic excipients rendered the cocrystal stable.[180,186,187] It should be pointed out that the majority of coformers employed in cocrystal research nowadays are acidic compounds, such as dicarboxylic acids; thus this issue can markedly impede market introduction of novel cocrystals. Risk assessment of cocrystal–excipient compatibility is necessary prior to clinical translation.

4. Future outlook

4.1 Development and characterization of alternative dosage forms for pharmaceutical cocrystals

Despite decades-long journey in cocrystal research, scarce attention has been directed at the preparation of alternative cocrystal dosage forms for uses outside oral use. Considering that the application of an oral cocrystal has become increasingly prevalent, one may adequately shift the focus to other dosage forms to expand the potential pharmaceutical benefits of the cocrystal. Reformulating APIs as alternative dosage forms *via* cocrystallization could bring synergy in solving problems associated with oral administration. This unique niche has been overlooked in the bulk of the existing literature. We herein provide an update on the feasibility of developing inhalable and topical cocrystal formulations.

4.1.1 Inhalable dry powder formulations. Direct delivery of a carrier-free cocrystal dry powder inhaler (DPI) formulation to the lungs manifests several prominent merits: 1) high local drug concentration, rapid onset of action, and bypass of first hepatic metabolism, which renders dose reduction possible and is particularly useful for targeting respiratory diseases; 2) apart from the dissolution advantage, cocrystallization can improve the aerosol performance (*i.e.*, particle size, dispersibility, and flowability) of APIs by selecting appropriate coformers; and 3) a high drug loaded DPI can be developed, as excipients intended to improve the aerosol performance of the drug may not be necessary.

Different methods have been reported for producing inhalable cocrystal DPIs, namely liquid assisted grinding,[188] milling,[189,190] spray drying,[92,188,191] and spray freeze drying.[192] It is widely recognized that particles with a mass median aerodynamic diameter (MMAD) between 1 and 5 μm

are ideal for deep lung delivery.[193] Hence, spray drying and spray freeze drying stand out as the most suitable techniques as one can manipulate the aerosolization attributes (*e.g.*, size, density, and morphology) by customizing different processing parameters in a reproducible, continuous, and scalable manner. However, the rapid drying kinetics may give rise to an unwanted amorphous product prone to unpredictable phase transformation during storage. Weng *et al.* reported the development of a spray-dried partially coamorphous itraconazole–suberic acid cocrystal DPI with a superior dissolution profile and size distribution compared with pure itraconazole.[92] Similarly, Ray *et al.* produced an coamorphous autophagy-inducing inhalable formulation of niclosamide–nicotinamide for lung cancer therapy.[191] Moreover, a coamorphous theophylline–oxalic acid cocrystal was generated by Tanaka *et al.* using spray freeze drying with an MMAD of 3.03 μm, which showed an improved hygroscopicity and reduced pseudopolymorphic transformation.[192] In contrast, Alhalaweh *et al.* demonstrated the possibility of obtaining highly crystalline inhalable theophylline (THP) cocrystals with urea (URE), saccharin (SAC), and nicotinamide (NIC) *via* spray drying.[189] THP–NIC had a higher fine particle fraction than THP, whereas the formation of THP–URE and THP–SAC cocrystals deteriorated the overall aerosol properties. This observation might be linked to the varied surface chemistries and dispersive surface energies inherent to different cocrystal systems.[189] The precise correlation between processing parameters and cocrystal properties, especially crystallinity and aerosolization performance, is essential from the viewpoints of quality control, which should be highlighted in future investigations.

4.1.2 Topical formulations. Topical formulations, which deliver drugs through the skin surface for local or systemic treatment, is an attractive alternative to oral administration by evading enzymatic metabolism in the liver or pH-dependent degradation in the gastrointestinal tract. The stratum corneum is known as the major resistance limiting drug permeation through the skin.[194] Approximately 25% of drug candidates in development pipelines exhibit low membrane permeability.[195] Traditional formulation strategies for enhancing the skin permeability of a drug include prodrug selection,[196] ion pair technique,[197] hydration effect,[198] chemical enhancers,[199] *etc.* More recently, a few studies have highlighted the capability of cocrystals in modifying skin permeability, and to date there are two patents regarding the transdermal patch containing naloxone and naltrexone cocrystals filed by the Pain Therapeutics Inc., implying the potential utility of topical cocrystals in clinical setting.[200,201] Transdermal drug delivery is a multi-step process involving dissolution and release of drug in the formulation, followed by a series of drug partitioning and diffusion in the stratum corneum and epidermis layer.[202] Based on the steady-state skin flux equation,[203] the cocrystal may fundamentally modulate skin penetration by 1) increasing drug solubility and/or diffusion coefficient in the skin; 2) improving the partitioning between the drug formulation and the stratum corneum, and; 3) increasing the degree of saturation of the drug in the formulation. The earliest investigation can be dated back to 2013 by Yan *et al.* who demonstrated a simultaneous solubility and *in vitro* skin permeability improvement of a polyethylene glycol 400 ointment containing antiviral acyclovir cocrystals through the use of dicarboxylic acid coformers with higher lipophilicity.[204] Topical cocrystal gels targeting inflammatory diseases, such as rheumatoid arthritis and psoriatic arthritis, have been of great interest in recent years.[205,206] Machado *et al.* reported the production of a meloxicam cocrystal suspension and gel with salicylic acid to overcome the high dose oral meloxicam toxicity issue, resulting in an increased permeability coefficient from 1.38 to 2.15 × 10^{-3} cm h^{-1}.[205] The permeation advantage provided by the cocrystal may correlate to the alteration of crystal structure, albeit rarely discussed. Sanphui *et al.* demonstrated the structure–permeability correlation of hydrochlorothiazide cocrystals with coformers of nicotinic acid, nicotinamide, and succinimide.[207] It was suggested that the absence of sulfonamide dimer/catemer synthons in the nicotinic acid and nicotinamide cocrystals gave rise to improved permeability.[207]

The effect of permeability modulation *via* cocrystallization is highly relevant to the choice of coformers. Apart from enhancing permeability, the potential of a sustained-release topical cocrystal was further highlighted by Rosa *et al.*[91] A drug–herb topical cocrystal formulation of the highly soluble isoniazid and the hydrophobic resveratrol was developed for cutaneous tuberculosis,[91] which reduced the *P* value by 10 times and the amount of permeated drug by 86% when compared with pure isoniazid. Notably, the idea of a topical cocrystal was recently conceived in cosmeceutical science. Ferulic acid, a common anti-aging skin care ingredient prone to physicochemical decomposition, was developed as a sustained-release topical oleogel cocrystal formulation with skin care-related coformers.[13] Viscosity has been shown to be inversely proportional to the *in vitro* drug release rate/*ex vivo* permeation rate of gel formulation.[208–210] Oleogel containing a ferulic acid–isonicotinamide cocrystal exhibited a 1.3-fold higher viscosity as a result of molecular reorganization compared with that containing pure ferulic acid, which may be one of the factors contributing to a slower permeation across the membrane.[13] Despite the promise, the application of cocrystals to transdermal therapeutic systems can be hampered by the inherent risk of cocrystal dissociation in liquid or semi-solid phases. Long-term stability studies of the topical cocrystal formulations under ambient conditions or short-term stability studies under accelerated storage conditions should be performed to eliminate any possible stability issues.

4.2 Emerging categories of pharmaceutical cocrystals

This section introduces several novel technologies in producing pharmaceutical cocrystals, which may represent

an important step forward in the efficient and expedited development of high-quality cocrystal tablet products of challenging drugs.

4.2.1 Nano-cocrystals. Nano-cocrystals are cocrystal particles which are nanosized, with a mean diameter of <1 μm.[211] Recently, nano-cocrystals have garnered increasing attention by virtue of their synergistic advantages offered upon integration of the two extensively explored crystal engineering strategies, *i.e.*, nanotechnology and cocrystallization. By downsizing the pharmaceutical cocrystals to a nanoscale, extra benefits on the fundamental properties of an API are anticipated in stark contrast to micronized cocrystals, ranging from thermosensitive luminescence,[212] mechanical properties,[213] physical stability,[214] dissolution rate,[215,216] *in vivo* bioavailability,[217,218] to reduced drug toxicity.[219]

Top-down (*e.g.*, ball milling, high-pressure homogenization) and bottom-up approaches (*e.g.*, precipitation, spray flash evaporation) have been exploited for nano-cocrystal preparation, including phenazopyridine–phthalimide,[215] paclitaxel–disulfiram,[220] caffeine–oxalic acid,[221] caffeine–phydroxybenzoic acid,[222] 4-aminosalicylic acid–sulfamethazine,[223] myricetin–nicotinamide[224] nano-cocrystals, *etc.* The rational design and production of nano-cocrystals is deemed more challenging than nanoparticles *per se* as one should further consider the preservation of the cocrystal integrity. Recently, Thakor *et al.* applied a quality by design approach to systematically prepare and optimize a nano-cocrystal of carbamazepine with nicotinamide by anti-solvent precipitation,[211] and figured out the significant formulation parameters affecting particle size. Pharmaceutical companies also evince interest to invest in this novel technology. Takeda Pharmaceutical Company Limited has been granted a patent in 2019 for the invention of a suspension containing a non-dissociable nano-cocrystal *via* wet grinding in water with a polymer and a surfactant.[225] Although its development is still in infancy, the extension of the utility of cocrystal engineering adds high value to the development of nanomedicine and, thus, may spark extensive attention in the foreseeable future.

4.2.2 Spherical cocrystals. Spherical crystallization (SC), invented by Kawashima *et al.* in the early 1980s,[226,227] enables the transformation of fine crystals directly into compact large spherical agglomerates during the crystallization process.[228–230] For a single-component system, SC effectively enhances different micrometric properties, such as tabletability, compressibility, powder flowability, packability, punch-sticking propensity,[231–235] *etc.* One of its potential drawbacks is the reduced surface area of particles exposed to dissolution media, thus retarding the drug release of poorly soluble APIs.[234] Commonly used approaches for SC include spherical agglomeration (*i.e.*, anti-solvent, pH shift, and direct methods)[226,236,237] and quasi-emulsion solvent diffusion (QESD).[238–240]

Surprisingly, this long known technique is underexplored in the field of pharmaceutical cocrystals. It is not ambiguous to reason that spherical cocrystallization (SCC) is eminently more powerful in offering compounding effects on property improvements, as it represents a truly integrated crystal and particle engineering strategy.[241] One of the pioneering studies by Pagire *et al.* produced two polymorphic forms of carbamazepine–saccharin spherical cocrystal agglomerate (SCA) and purified them by means of selective agglomeration depending on the relative interaction between different bridging liquids and the crystal surfaces.[242] It was also applied to produce vitamin C cocrystals using vitamin B9 gels as pH switchable media for stoichiometry and particle size-controlled SCC.[243] More recently, Chen *et al.* for the first time highlighted the potential of SCC in simultaneously improving the manufacturing and dissolution performance of a poorly soluble drug griseofulvin in high dose (55.7%) direct compression tablets with acesulfame.[241] Similarly, high-drug loading tablet formulations comprising 46.3% and 41% of the poorly soluble drugs indomethacin and piroxicam with excellent flowability and enhanced dissolution performance were successfully developed by forming SCC with saccharin and ferulic acid, respectively.[244,245]

4.2.3 Dual-drug ternary cocrystals. Current cocrystal screening is generally on a trial-and-error basis, suggesting that one cannot freely choose any two drugs to cocrystallize. Discovery of many drug–drug cocrystals is therefore serendipitous, where the combination of coformers may not be clinically relevant in real life. To tackle this, which is extremely useful for a pair of drugs dilemma, dual-drug ternary cocrystals emerge as a novel strategy for designing multi-drug solid forms that are unable to directly cocrystallize because of a lack of complementary intermolecular interaction sites. It however remains challenging because a suitable bridge, which ideally possesses two or more hydrogen bonding sites adaptively matched with the APIs, may not be easily identified.[246] Liu *et al.* employed such a "drug-bridge-drug" strategy to cocrystallize the two first-line antitubercular drugs isoniazid and pyrazinamide using the bridge molecule fumaric acid, *i.e.*, the linker.[246] The ternary cocrystal exhibited improved pharmacokinetic properties compared with the parent drugs, conferring potential synergistic effects on killing *Mycobacterium tuberculosis* and minimize resistance.[246] Other reported ternary cocrystals include acetazolamide–nicotinamide–2-pyridone,[247] piperazine–ferulate–pyrazinamide,[248] and levetiracetam–isonicotinamide–calcium chloride[249] cocrystals.

5. Conclusions

An exponential growth in the number of publications on the topic of pharmaceutical cocrystals signifies the importance of cocrystallization in the medical field. This review presented the design principles currently employed in cocrystal screening. The benefits offered by cocrystallization, from fundamental to novel properties modification, were discussed. Challenges associated with cocrystal stability must

be solved before it can be broadly implemented to develop commercial pharmaceutical products. To date, the cocrystal products on the market are all oral tablets. We have thus highlighted the potential future development of alternative cocrystal dosage forms (*e.g.*, inhalable cocrystal DPI and topical cocrystal gel) and emerging classes of cocrystals that may be a future game changer in this field. It is eagerly anticipated that more regulatory approval will be granted to pharmaceutical cocrystal products, allowing clinical translation from the bench to the bedside.

Author contributions

Si Nga Wong: writing-original draft, visualization, conceptualization. Yu Chee Sonia Chen: writing-original draft. Bianfei Xuan: writing-original draft. Changquan Calvin Sun: writing-review & editing. Shing Fung Chow: conceptualization, supervision, project administration, writing-review & editing.

Conflicts of interest

There are no conflicts to declare.

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